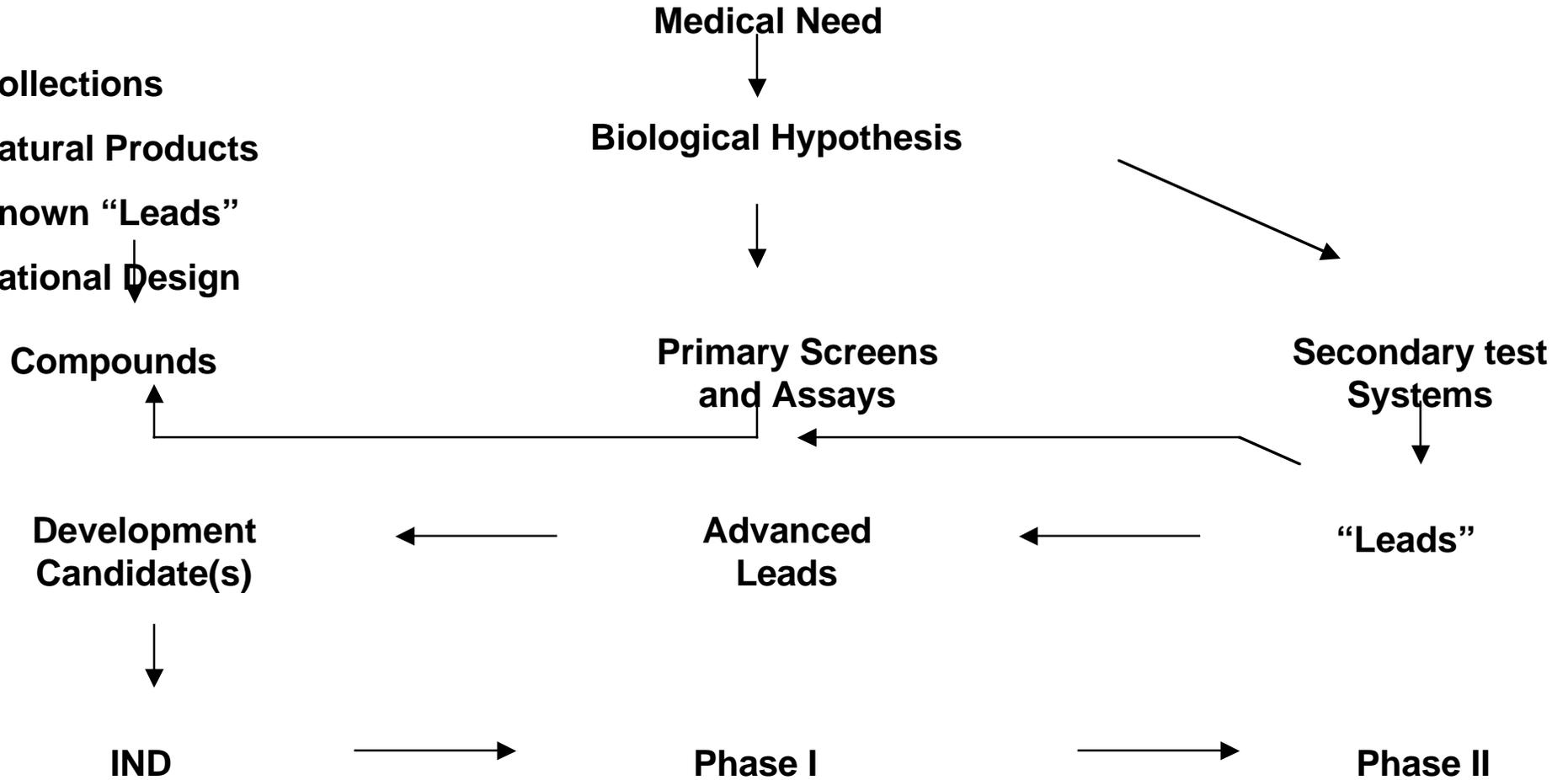


The New Millennium of Drug Discovery

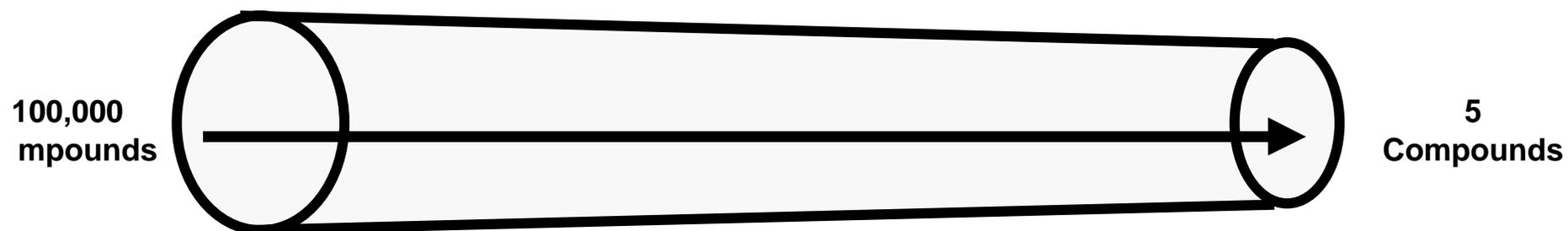
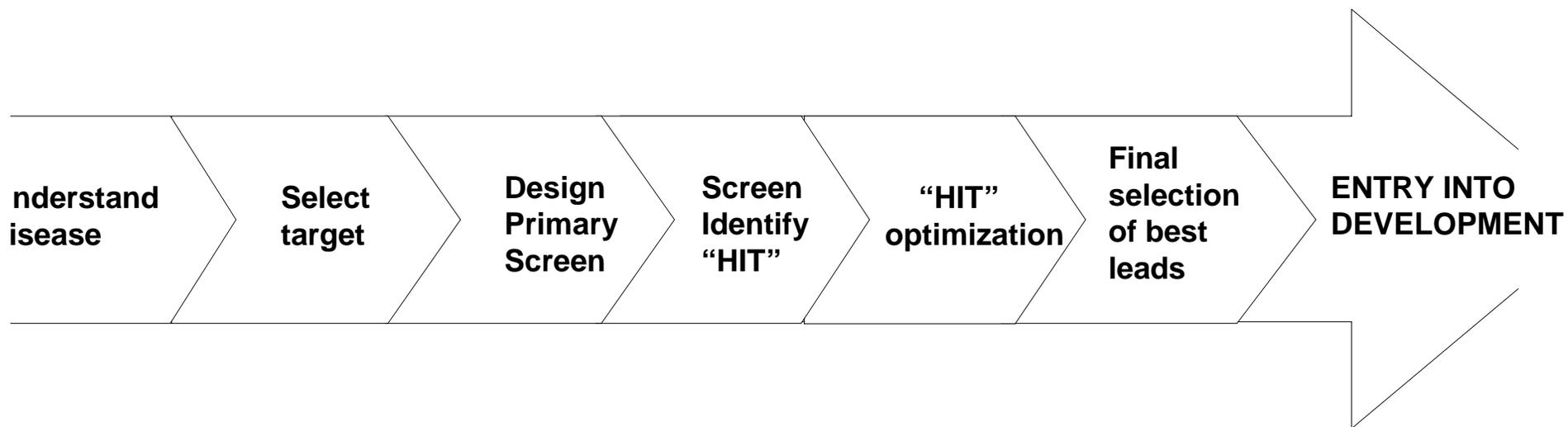
March 21, 2001

Drug Discovery Process

- Collections
- Natural Products
- Known "Leads"
- Rational Design



Drug Discovery Funnel



Enabling Technologies

- Genomics
- Combinatorial Chemistry
- High Throughput Screening
- Computer Assisted Drug Design
- Informatics
- Transgenic Animal Models of Disease

Genomics Strategy

- Identify new molecular targets
- Speed drug discovery
- Facilitates clinical development
- Genetics based patient selection

Combinatorial Chemistry

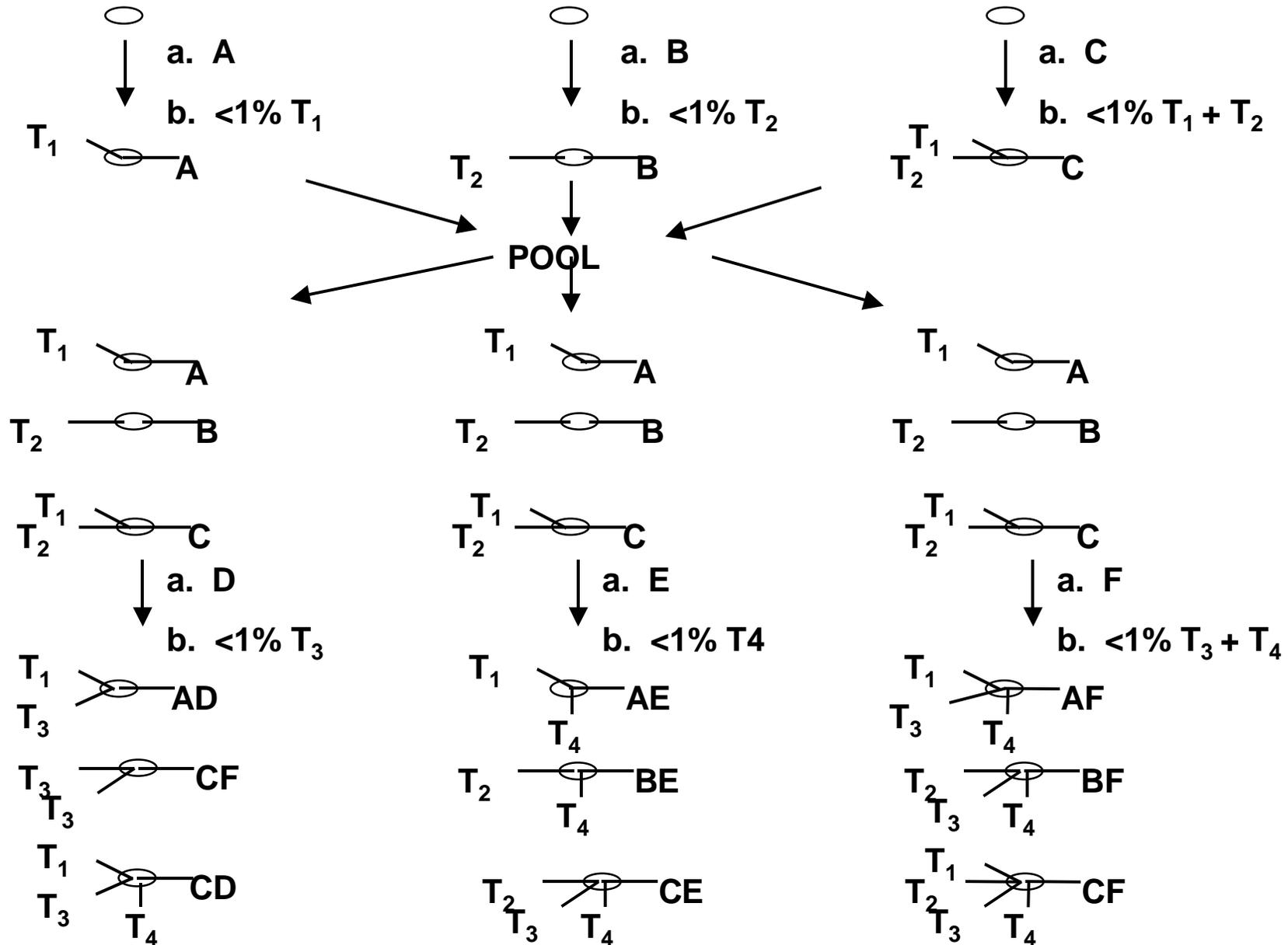
- A synthetic strategy
- Capable of producing large chemical libraries
- Libraries composed of diverse, non-biased structural entities
- Libraries composed of diverse structural entities based on a parent template

Size of Combinatorial Libraries

No. Synthons (Step 1) x No. Synthons (Step II x ...
No. Synthons (Step n) = No. Members

	<u>Steps</u>	<u>Members</u>
20 Synthons (e.g. natural amino acids)	3	$20^3 = 8 \times 10^3$
	4	$20^4 = 1.6 \times 10^5$
	5	$20^5 = 3.2 \times 10^6$
100 Synthons	3	$100^3 = 1 \times 10^6$
	4	$100^4 = 1 \times 10^8$
	5	$100^5 = 1 \times 10^{10}$

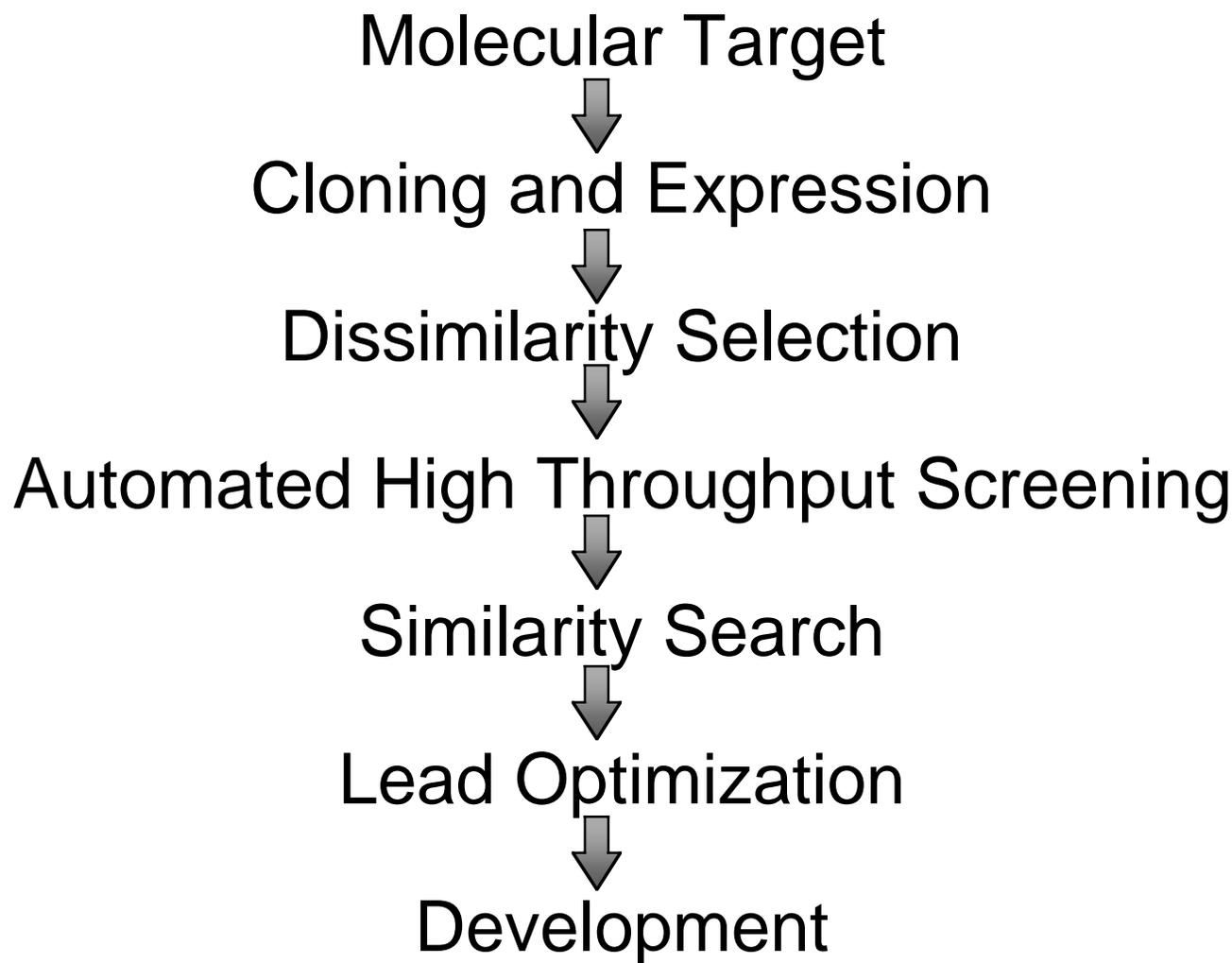
Binary Encoded Synthesis



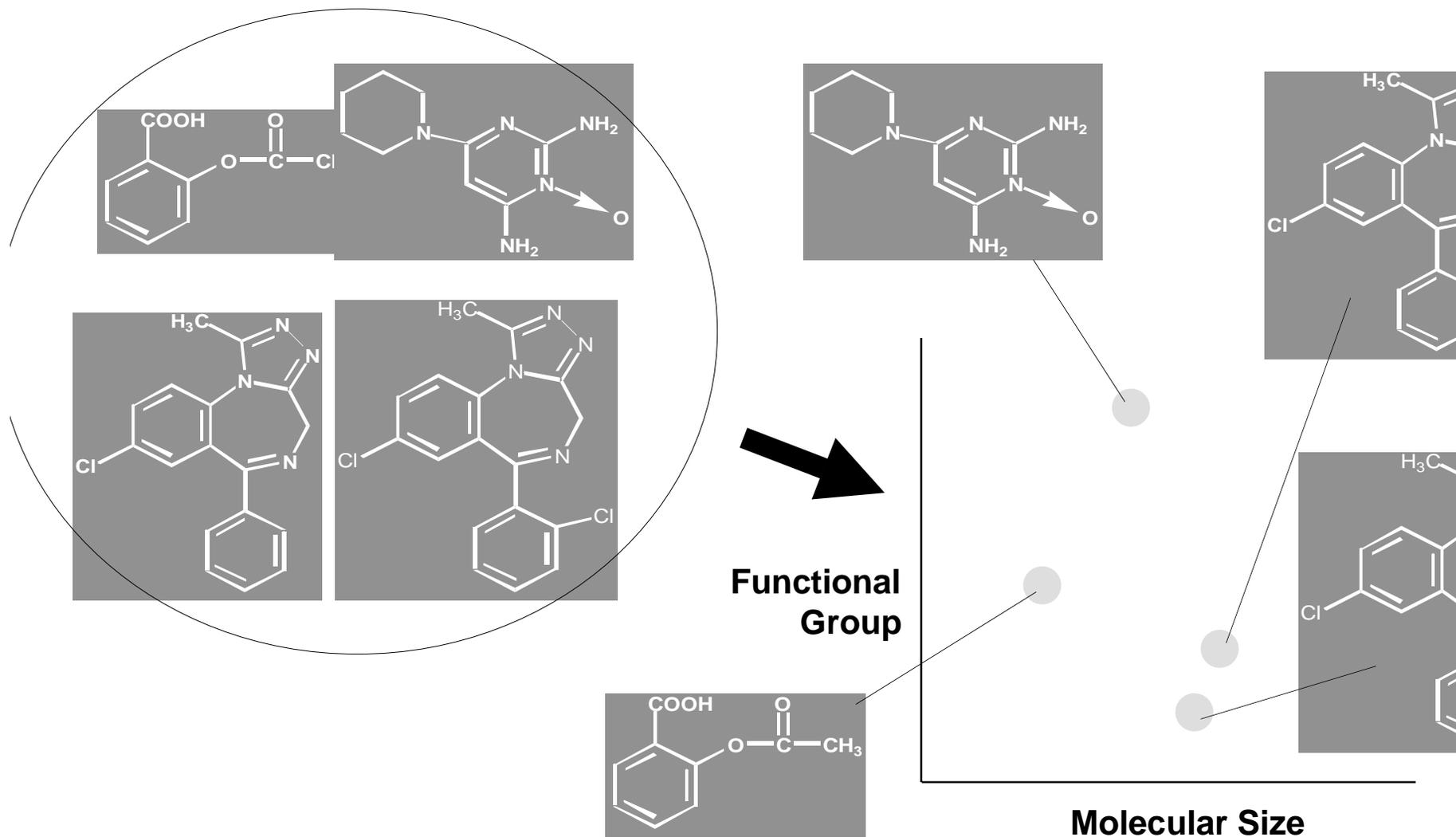
Limitations

- Large compound libraries require dereplication of “hits” (labor intensive)
- Characterization of “hits” is possible for peptide and oligonucleotide libraries...but resulting templates are presently of limited value
- Dereplication and characterization of non-peptide libraries is a challenge

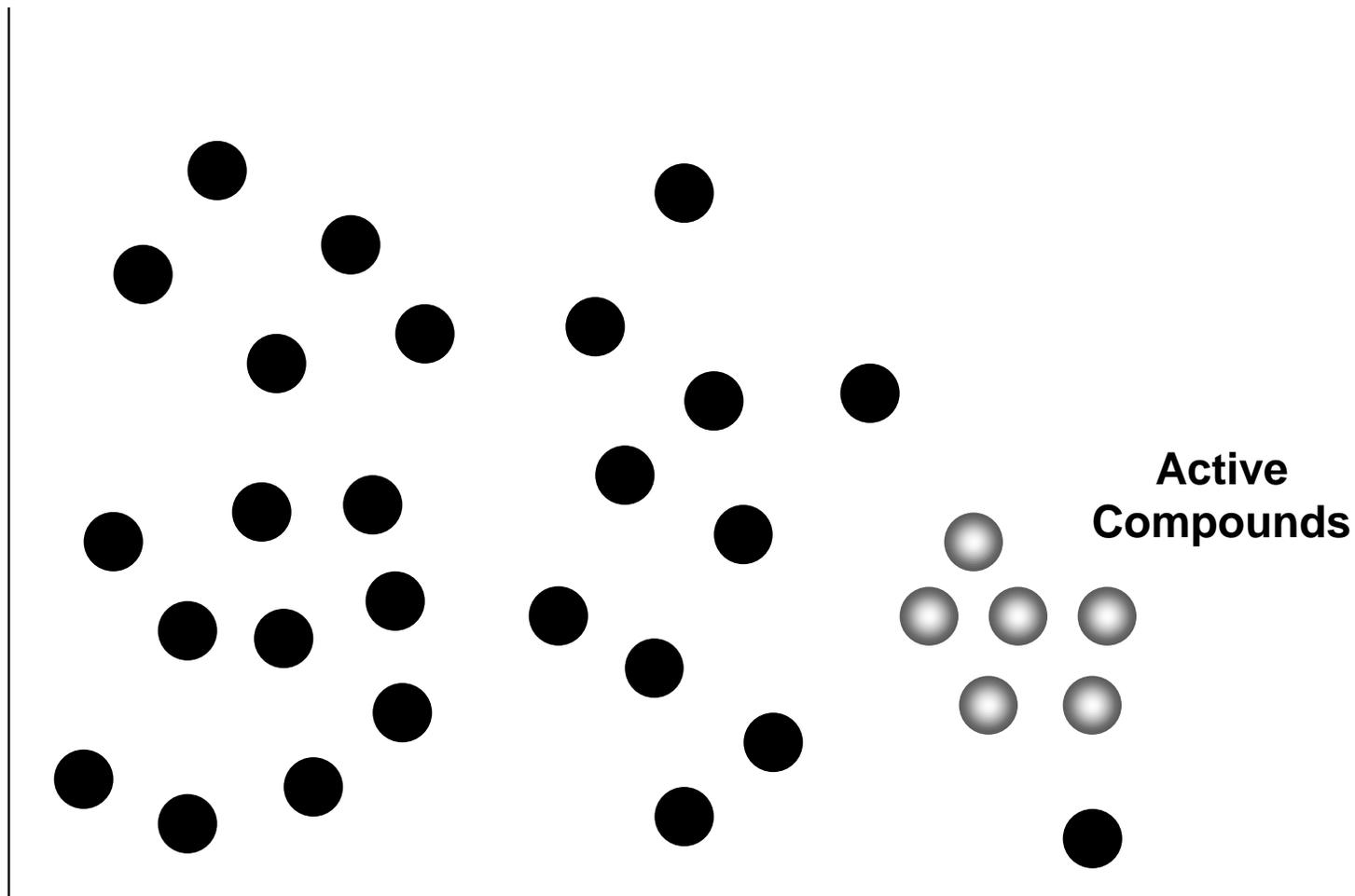
The Molecular Paradigm



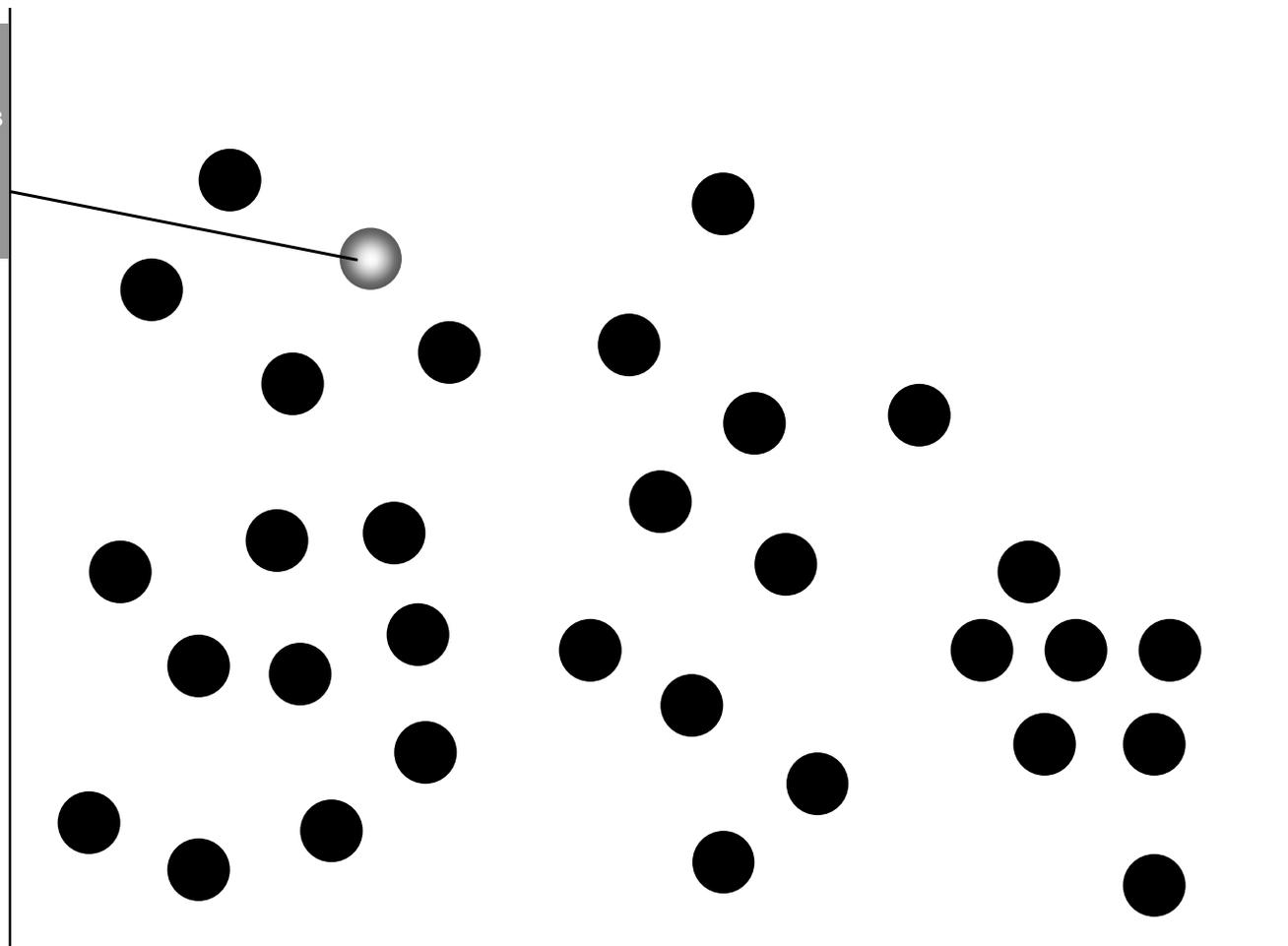
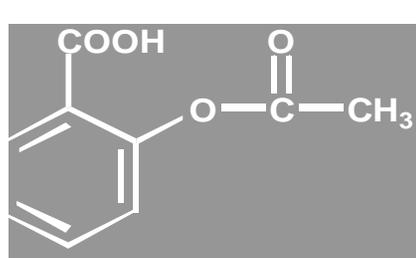
Describing Chemical Structure Information



Active Compounds in Our Database

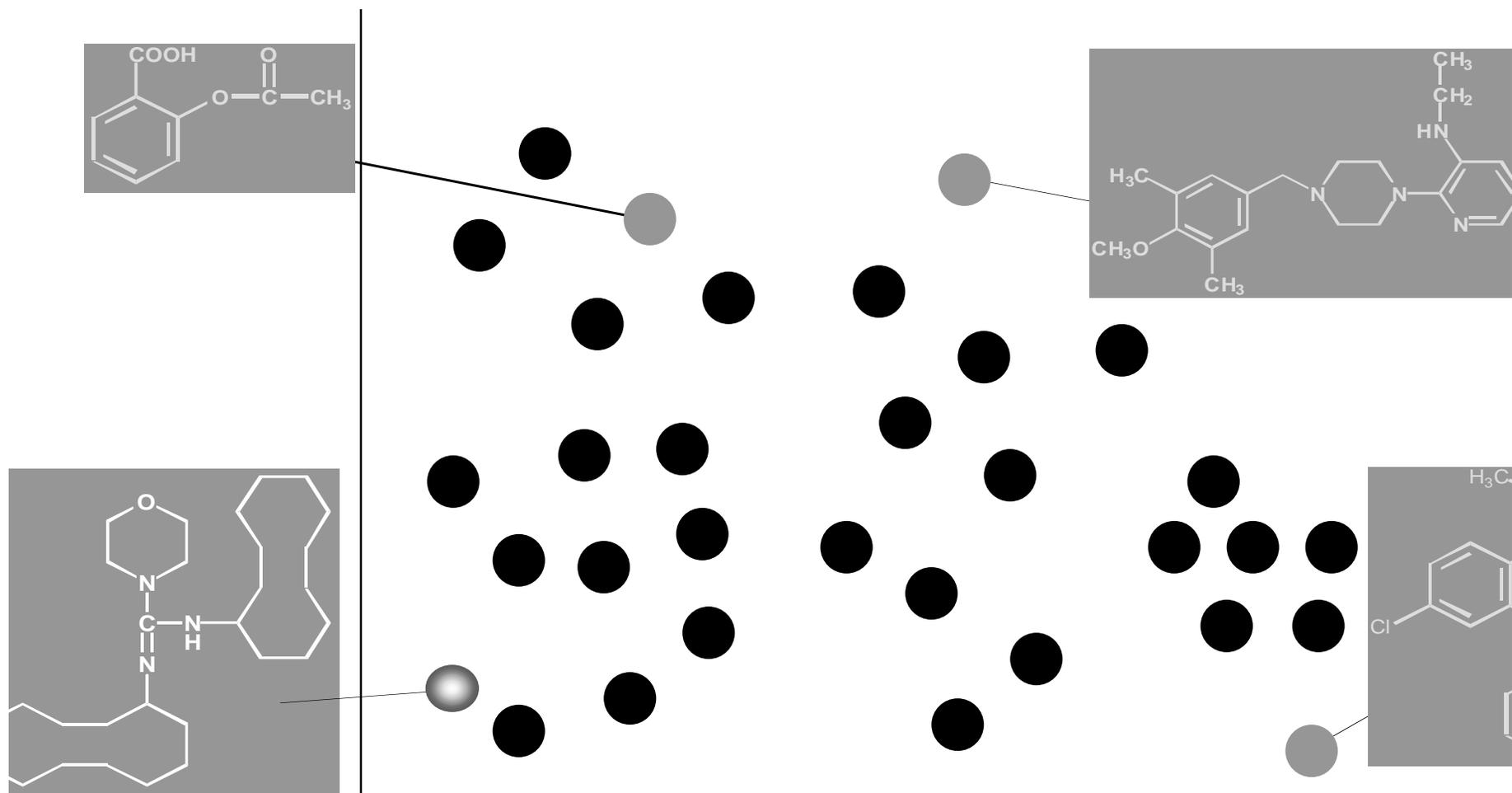


Dissimilarity-Based Compound Selection



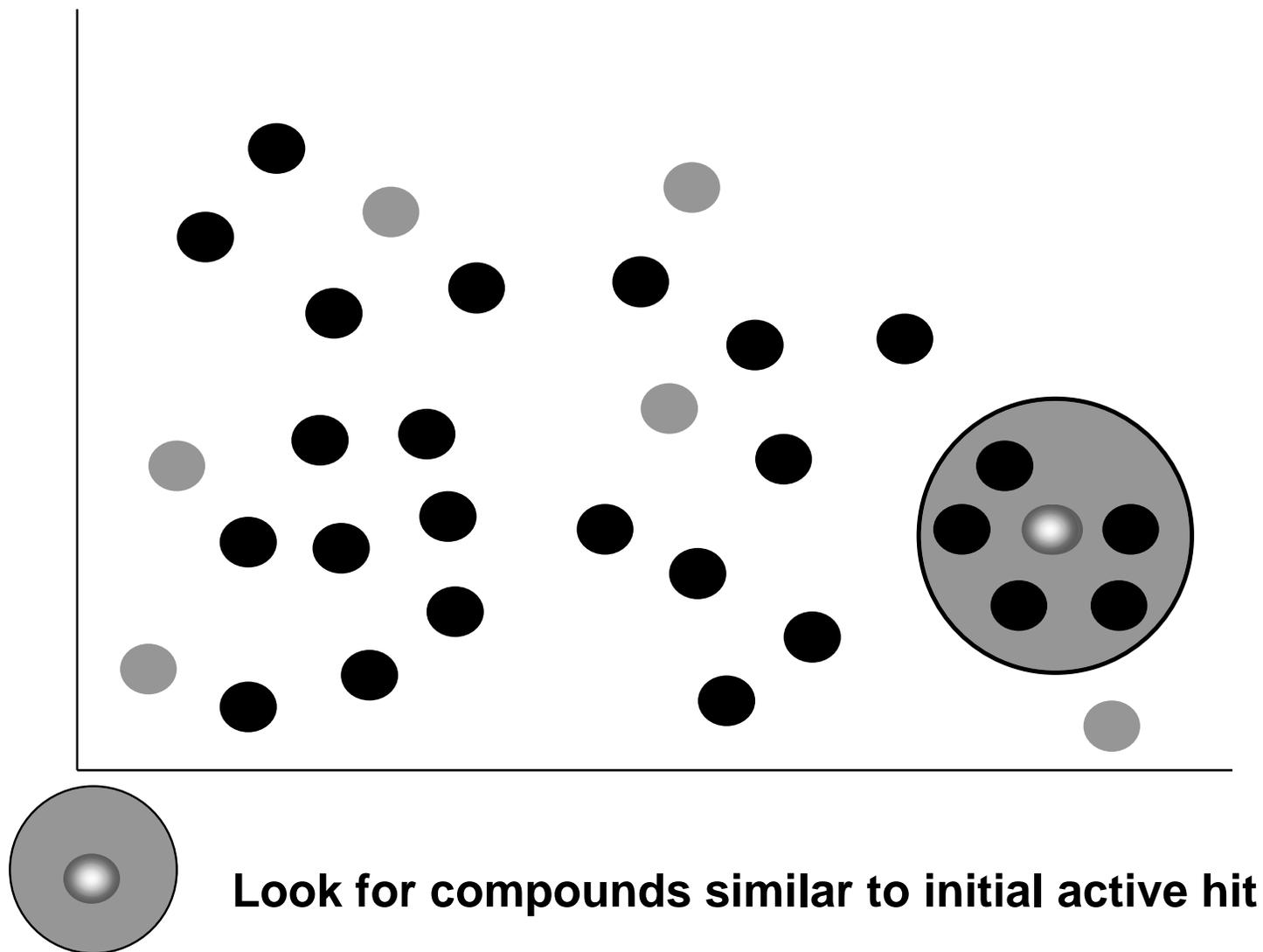
 1st compound selected for screening

Dissimilarity-Based Compound Selection

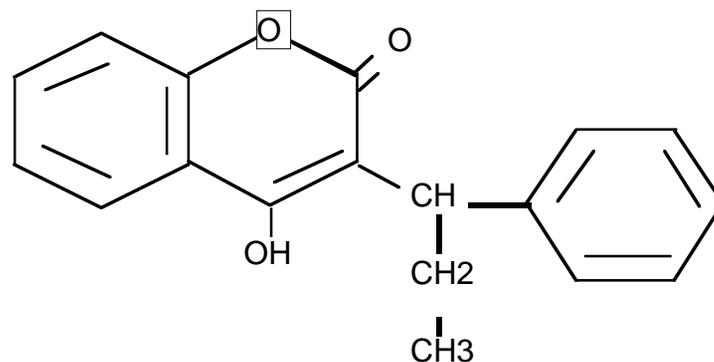


● 4th compound selected for screening

Similarity-Based Compound Selection

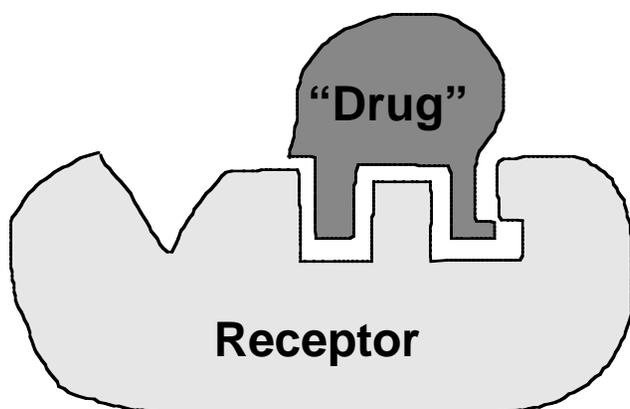


Phenprocoumon PNU-29342

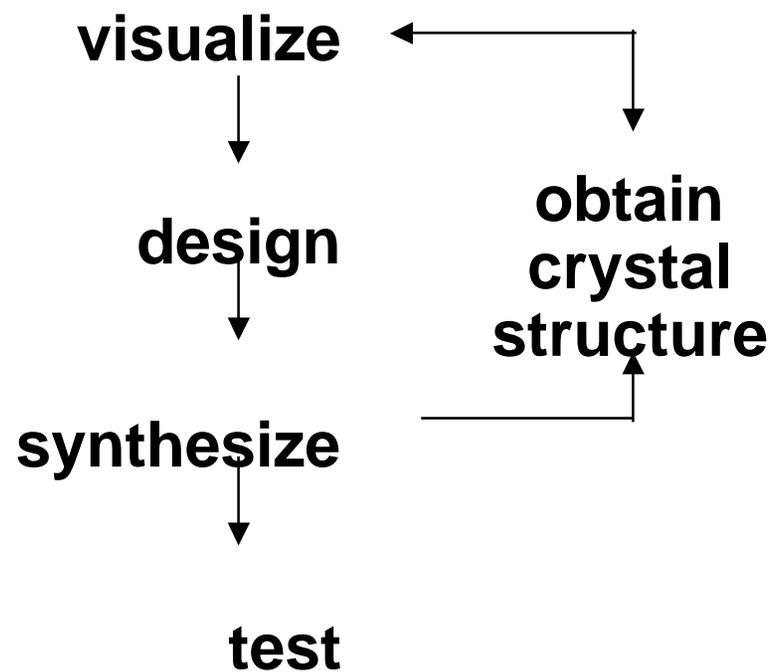


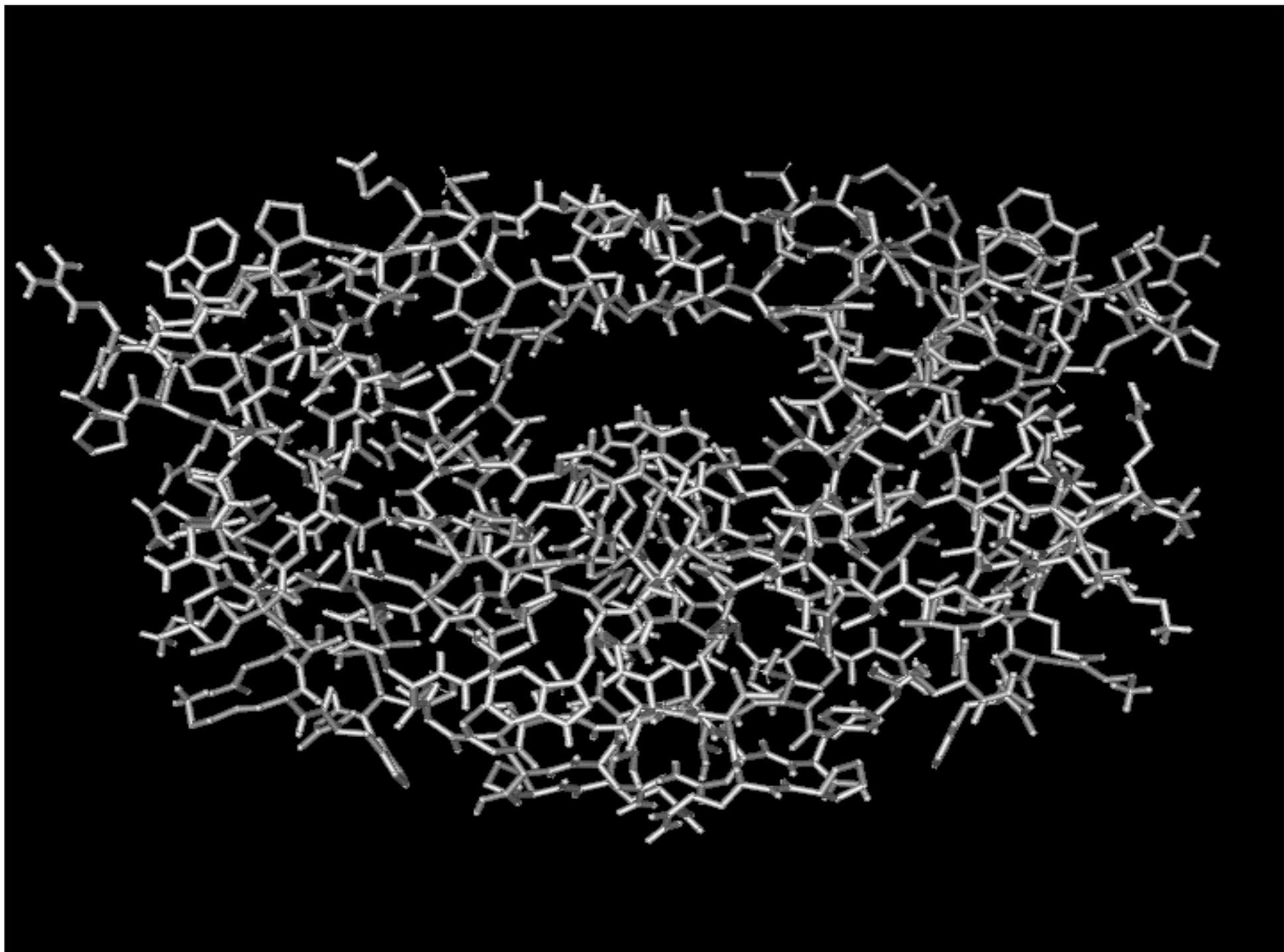
- Competitive Inhibitor
- $K_i \sim 1 \text{ m M}$
(HIV-1 and HIV-2 Proteases)
- $ED_{50} \sim 100 - 300 \text{ m M}$
(HIV-1 infected human PBL)
- Crystal Structure in HIV-1 Protease

Lock and Key View of Drug Receptor Binding

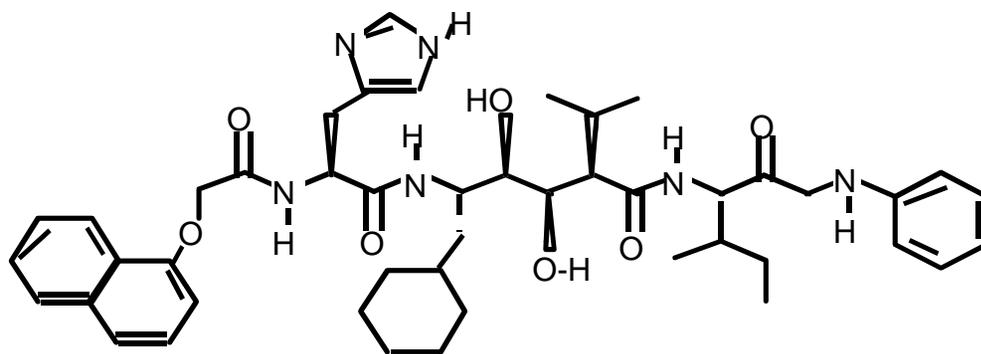


Iterative Structure-Based Design Paradigm



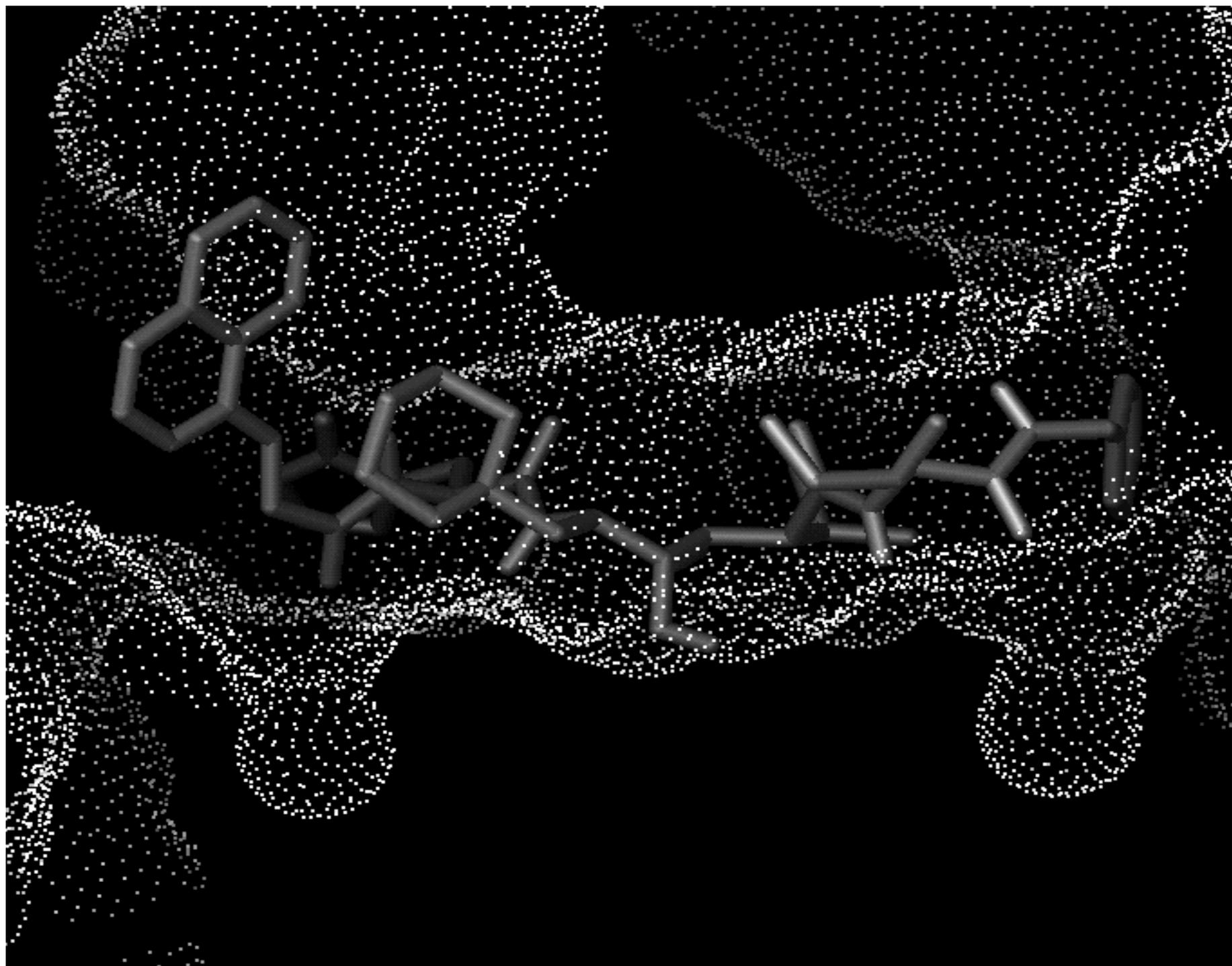


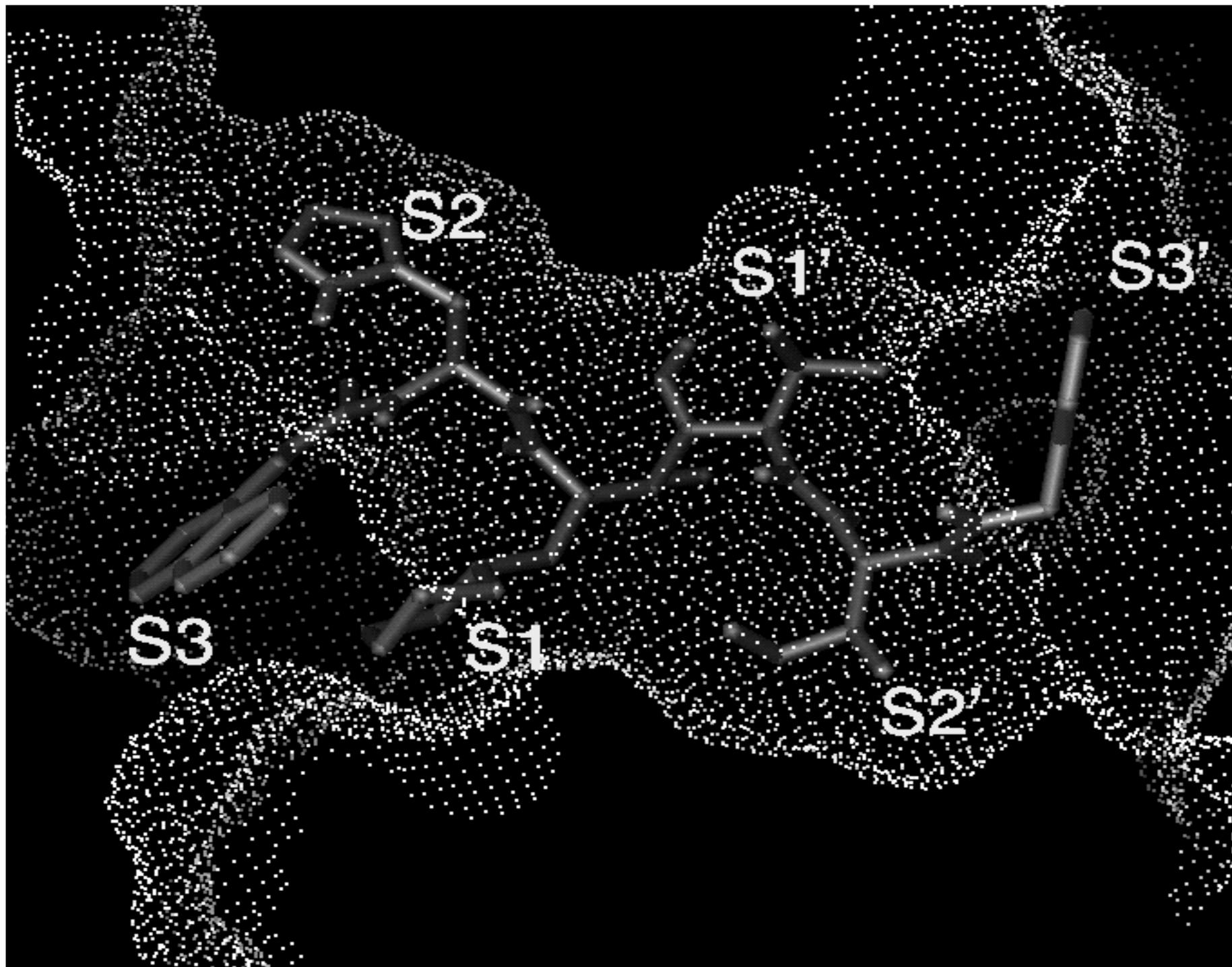
peptide Mimetic Protease Inhibitor

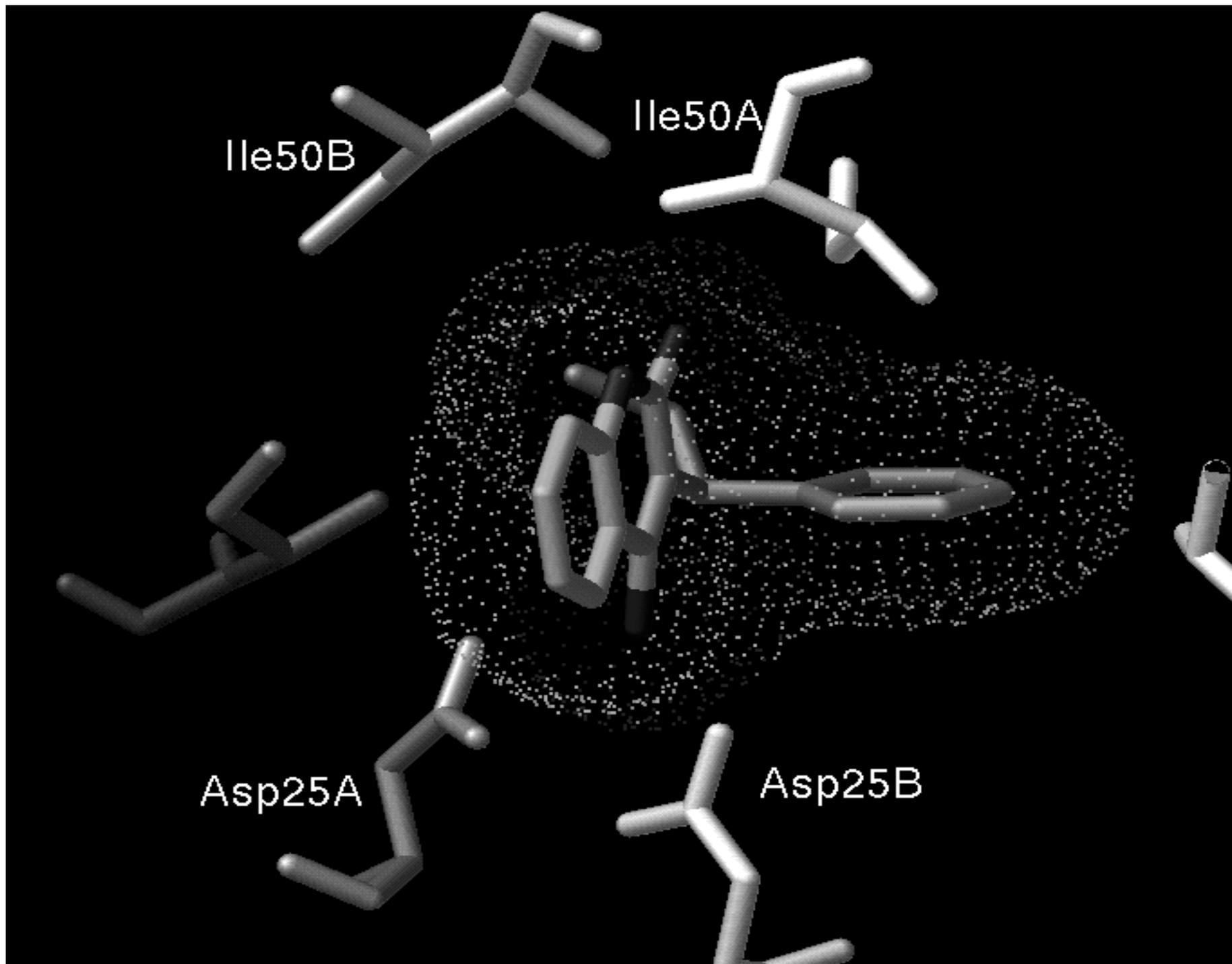


PNU-75875

- Potent enzyme inhibitor ($K_i < 1$ nM)
- Potent antiviral in cell culture ($IC_{50} < 10$ nM)
- Poor pharmacokinetic properties
- Complicated synthesis

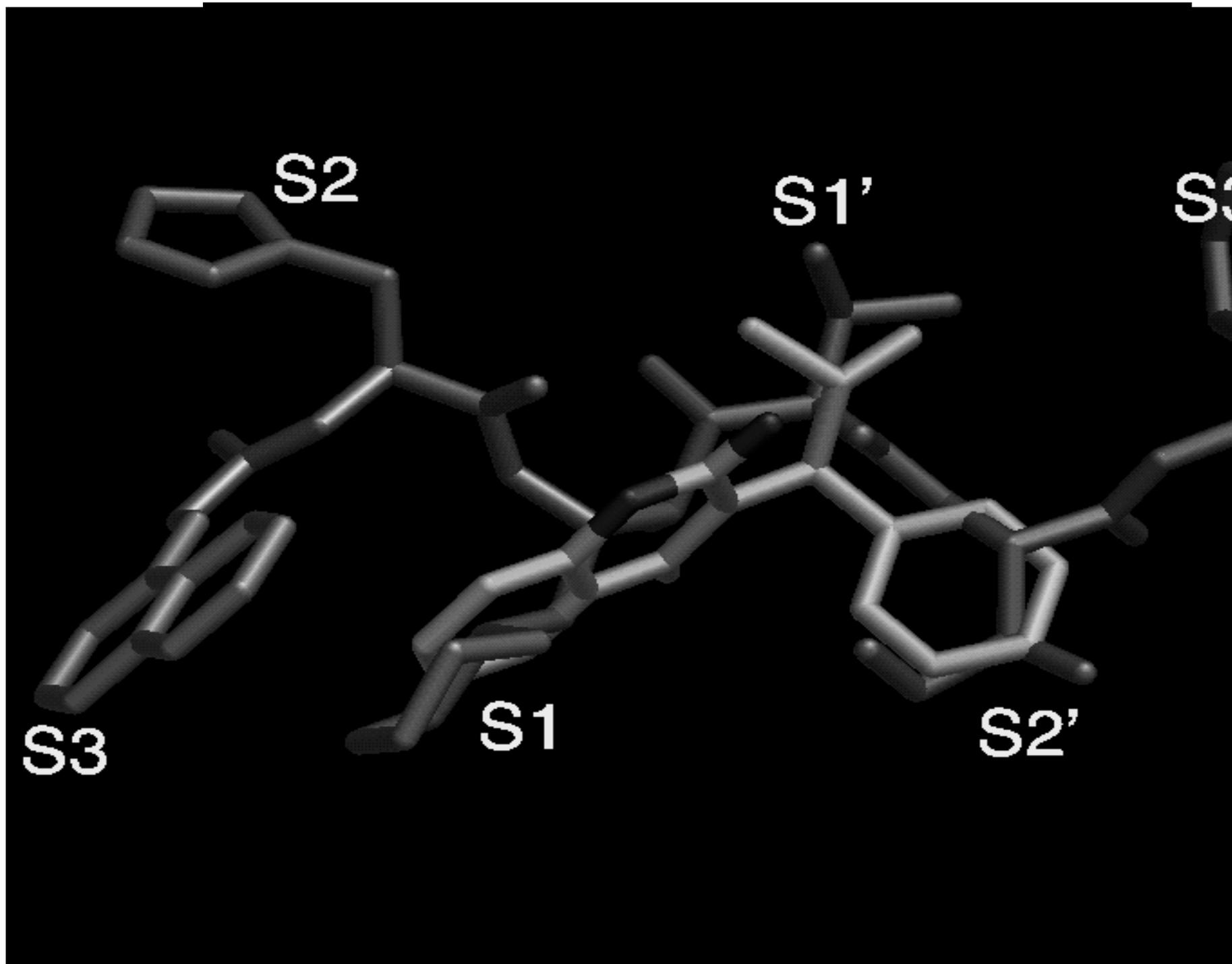


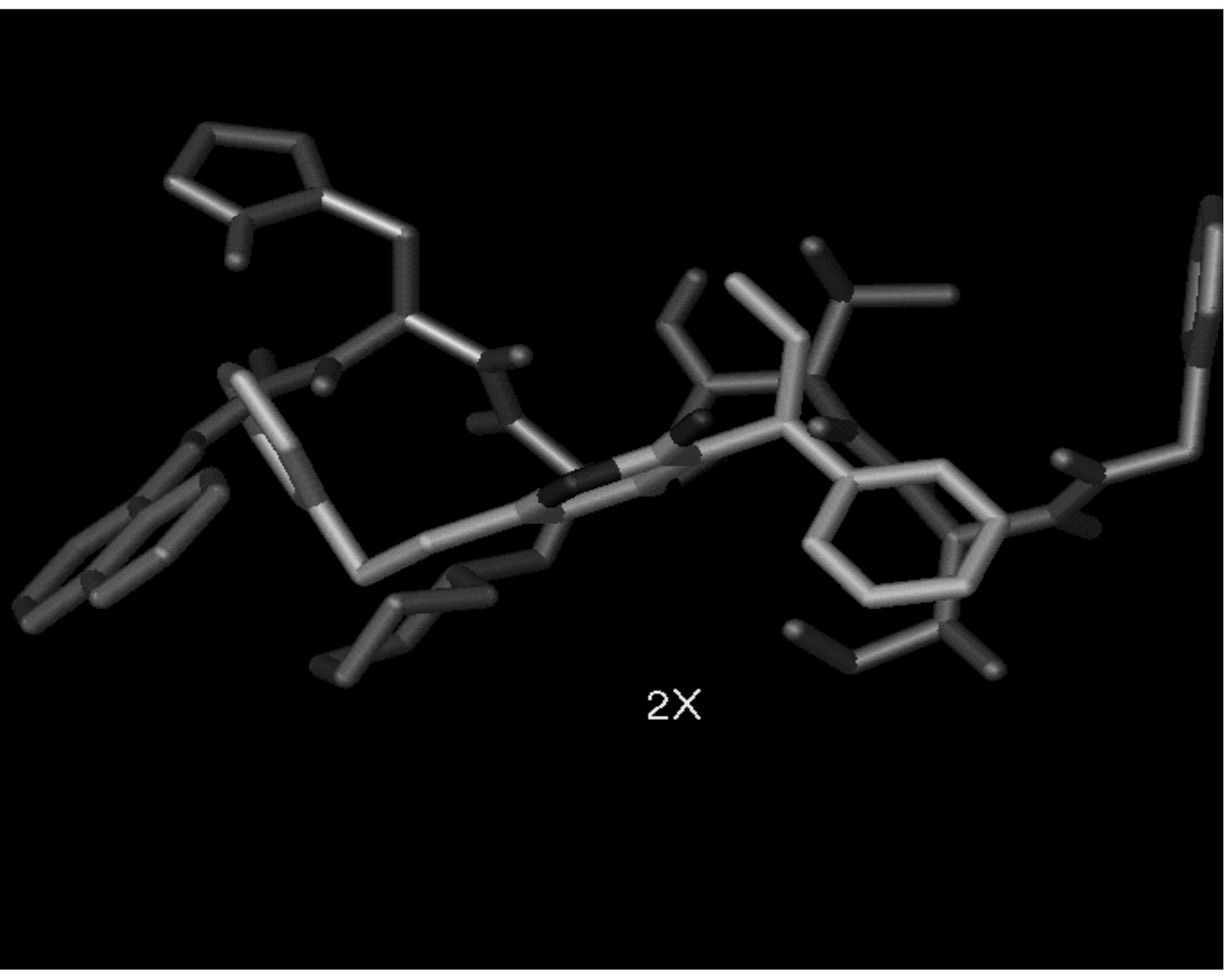




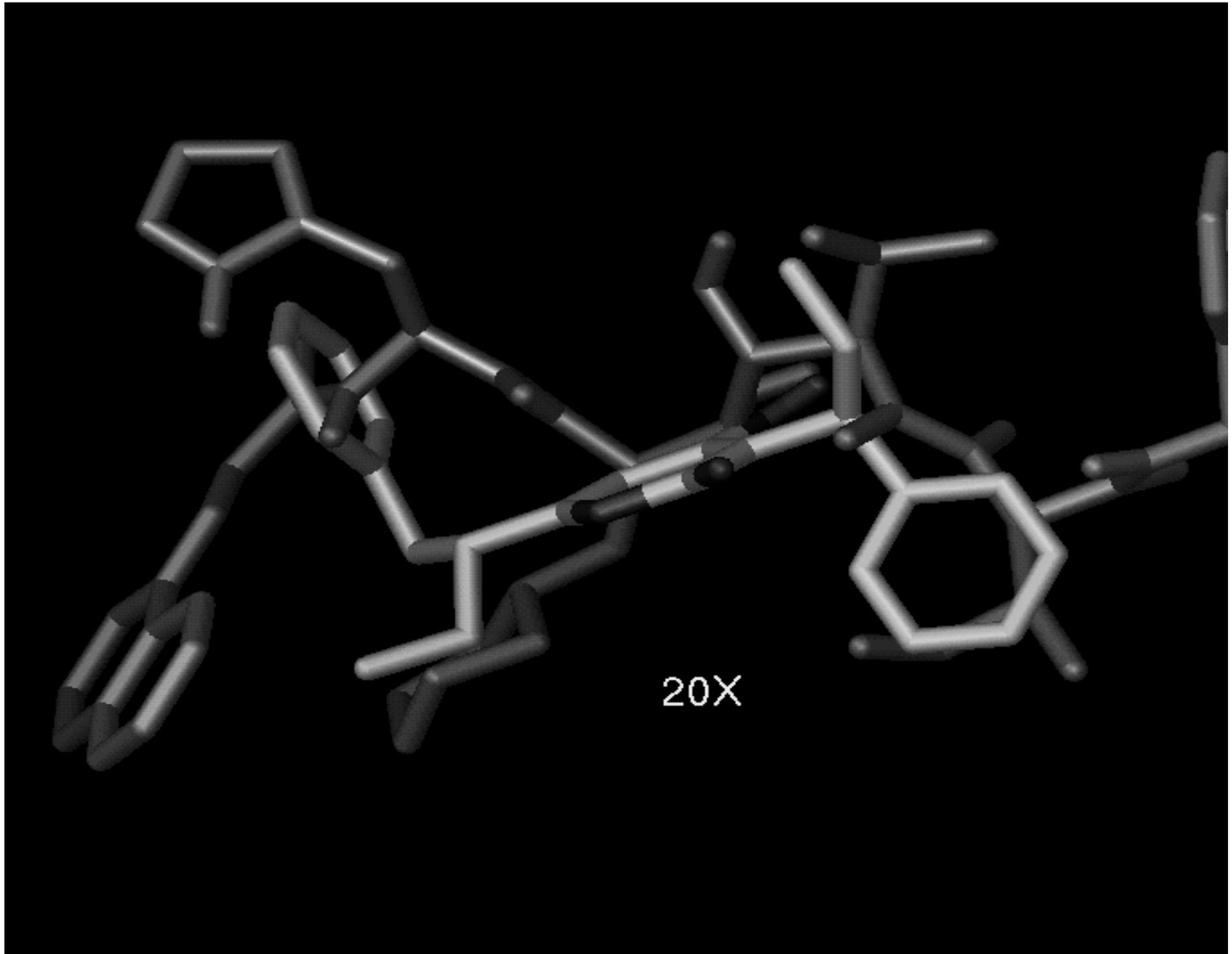
9342

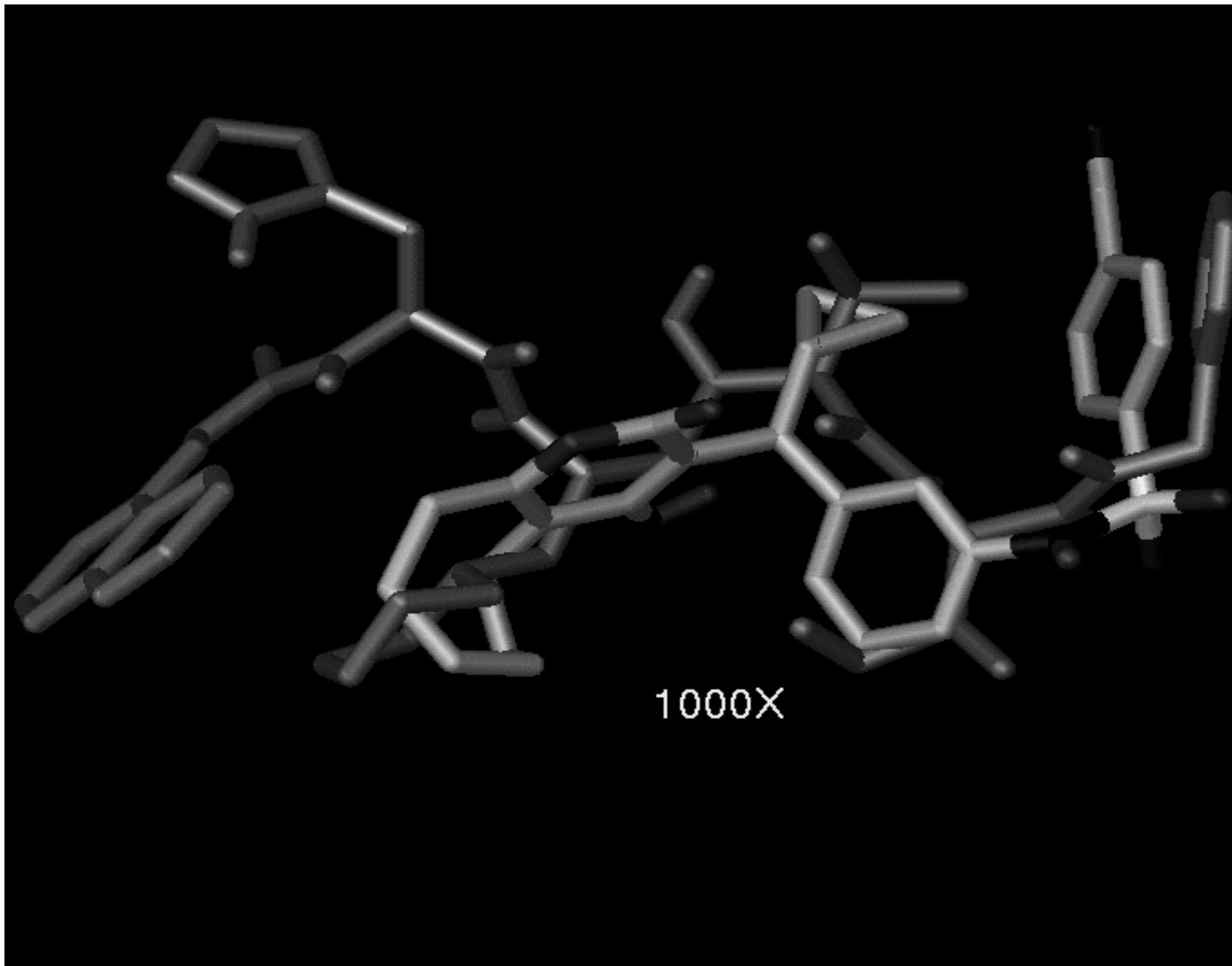
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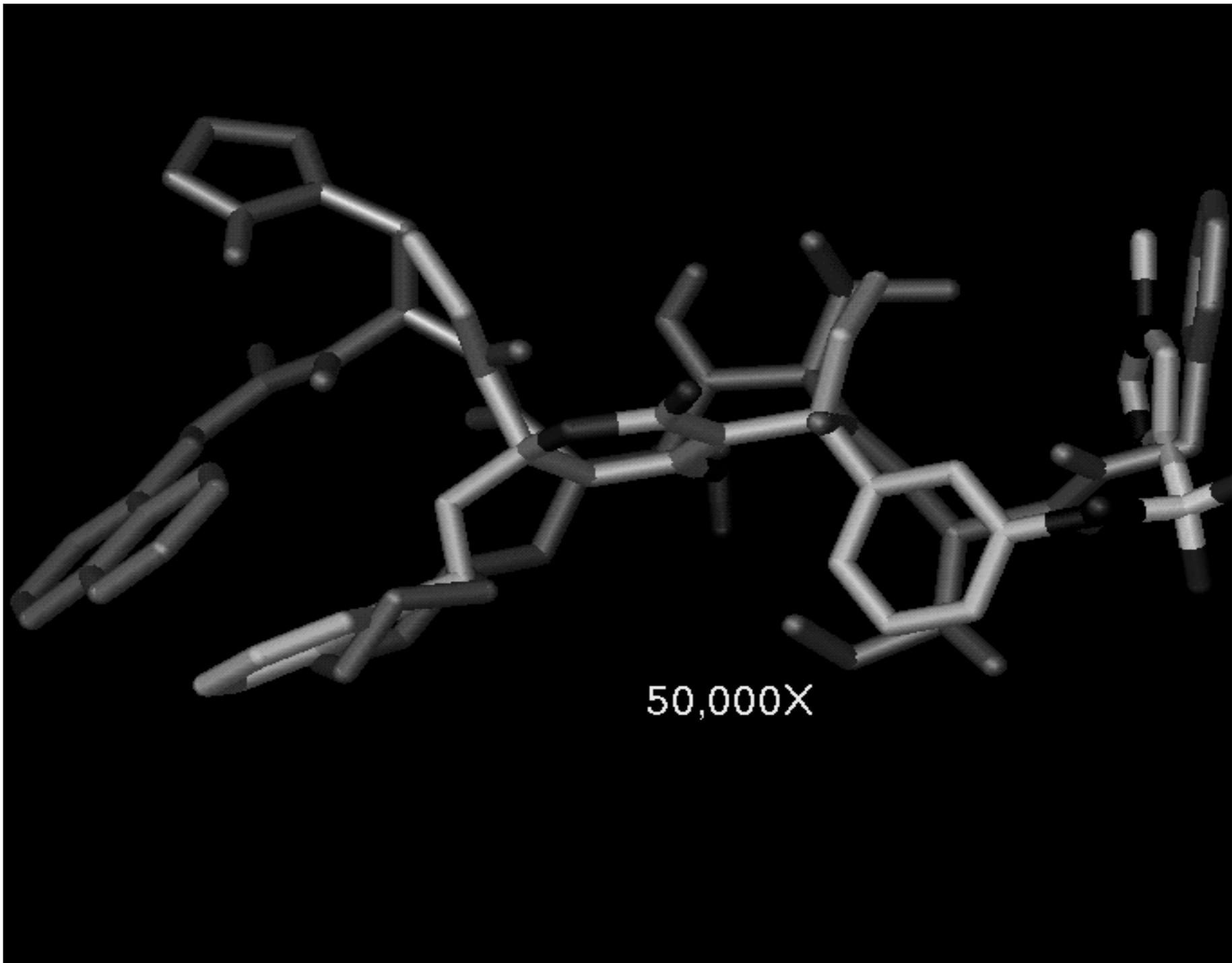


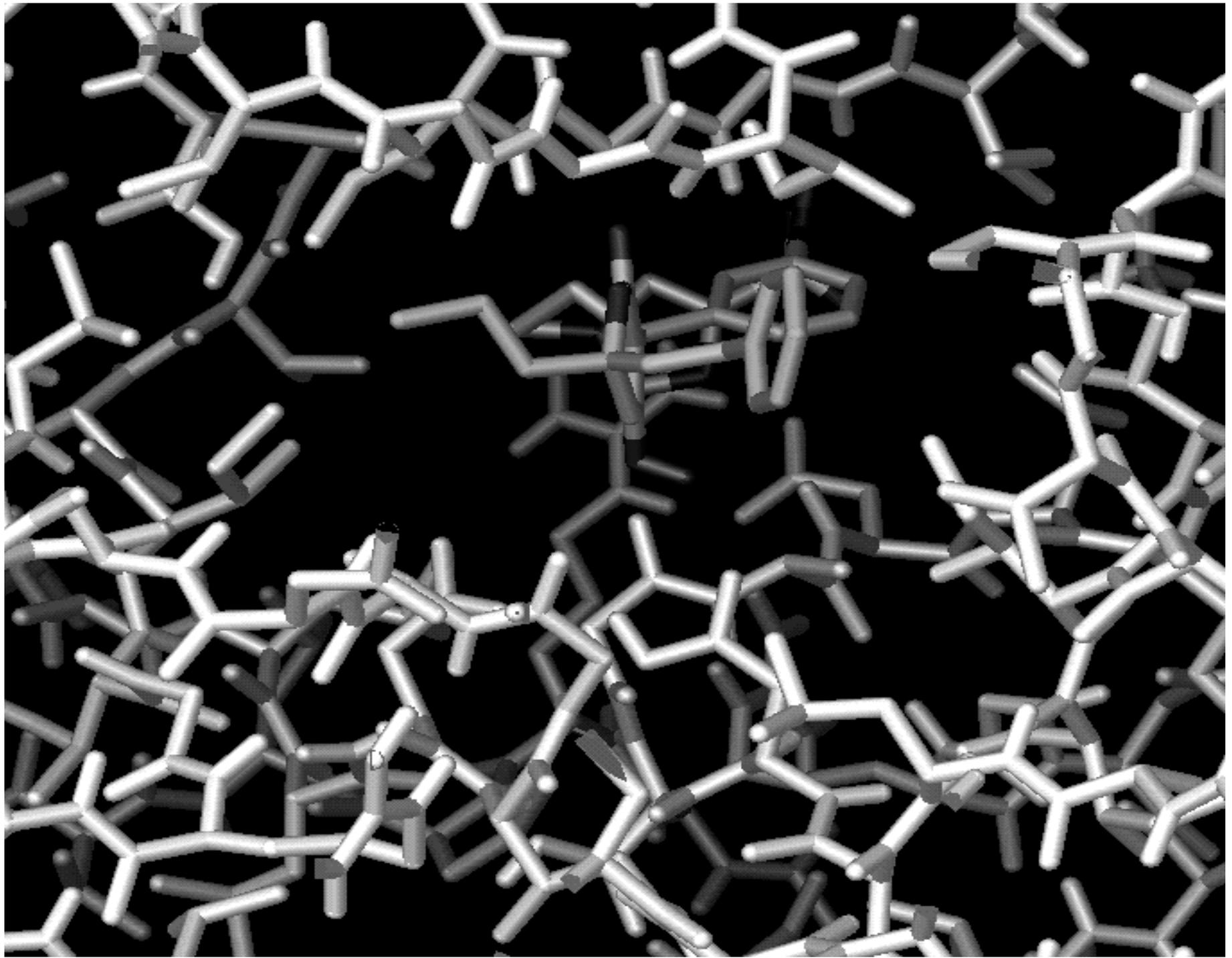


2X





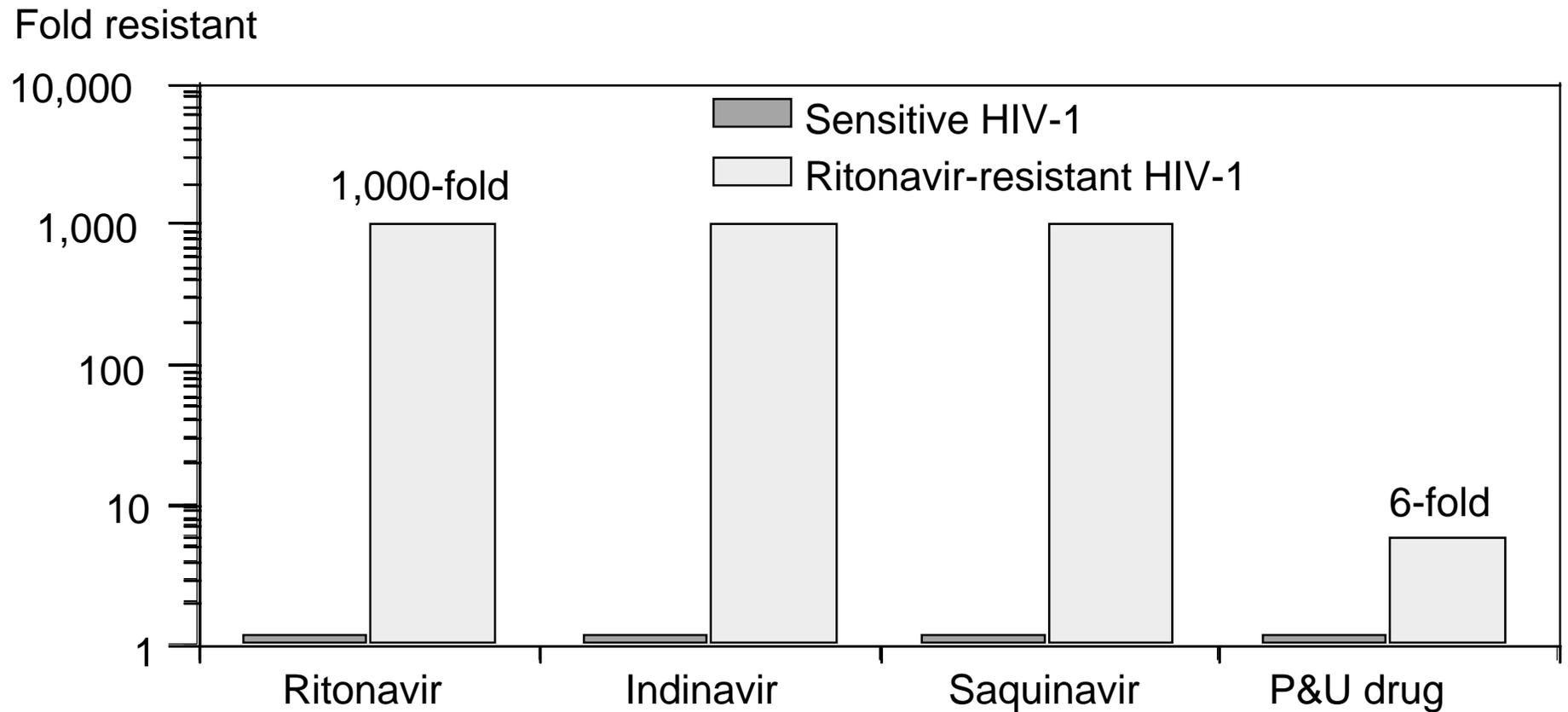




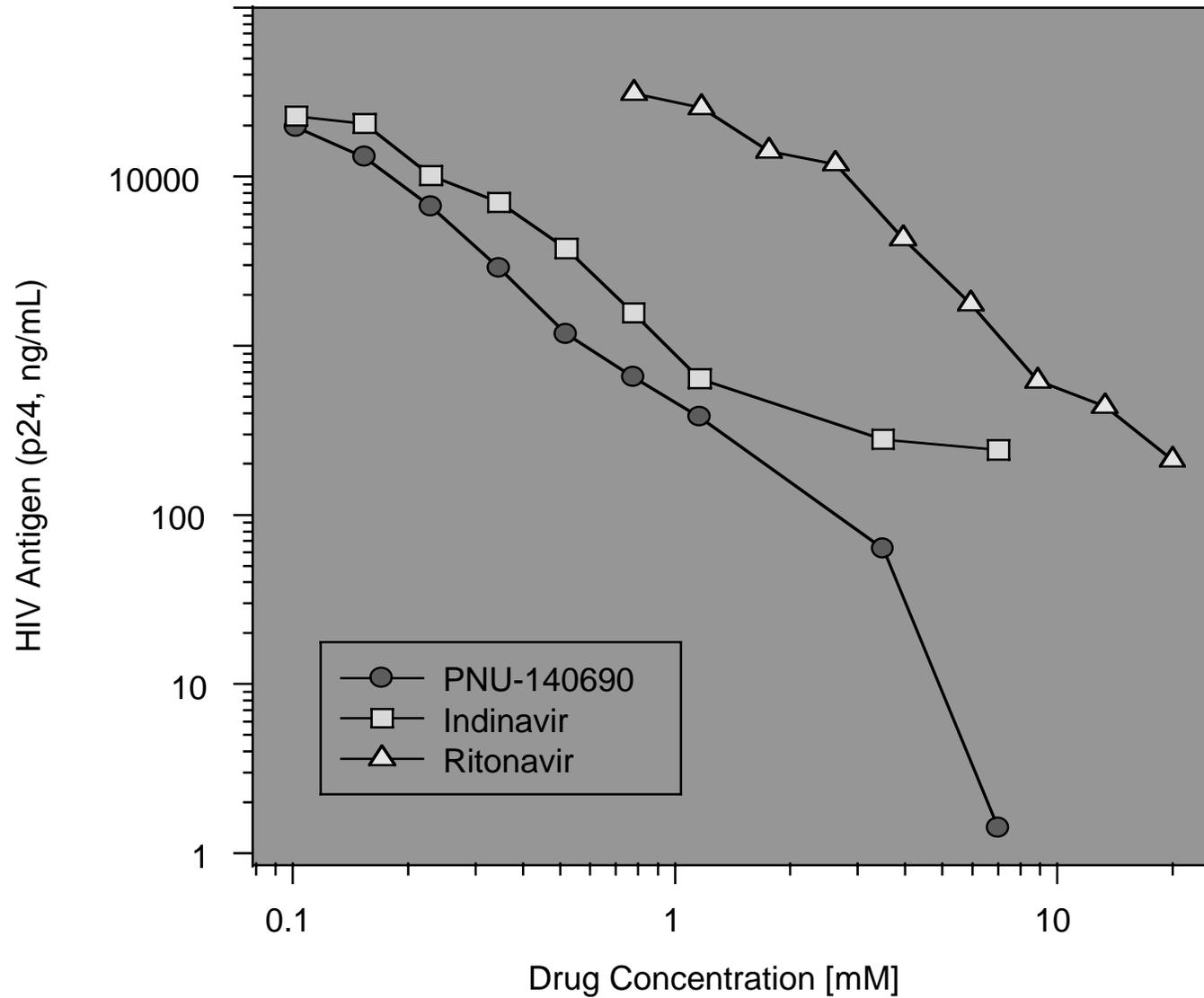
Protease Inhibitors Potently Block HIV-1 Replication

Isolate	IC ₉₀ (mM)	
	AZT	PNU-140690
UJ00004	≥5	.08
UJ00007	1.5	.15
UJ00009	1.8	.32
N. Amer1	2.5	.17
N. Amer2	≥5	.17
N. Amer3	≥5	.07
N. Amer4	≥5	.15
N. Amer5	≥5	.17
N. Amer6	≥5	.12
N. Amer7	3.5	.16
Mean IC₉₀ ± SD	>5	.15 ±.07

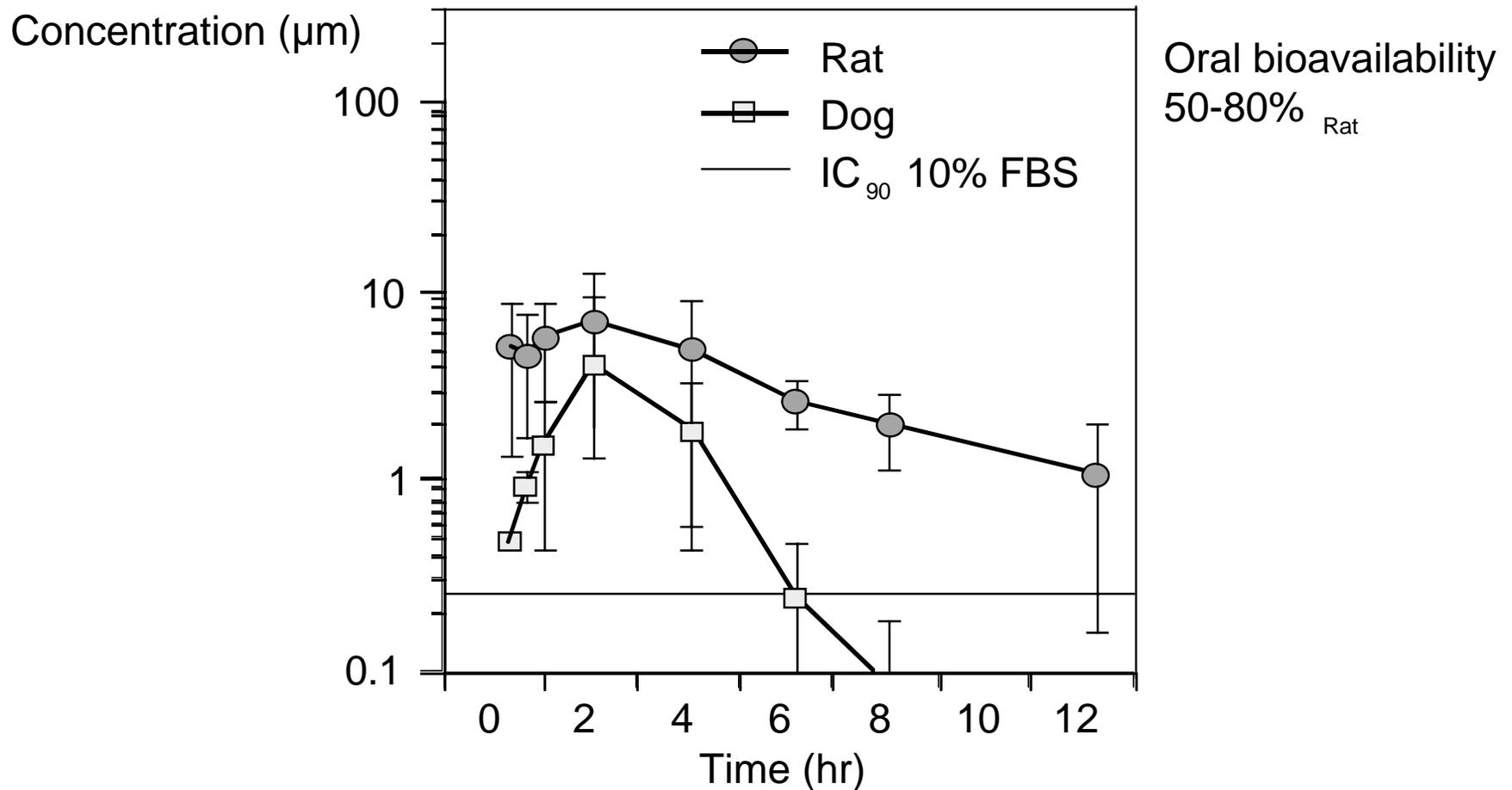
Inhibitors are not Cross-Resistant with their Protease Inhibitors



PNU-140690 Blocks Replication of Ritonavir Resistant HIV



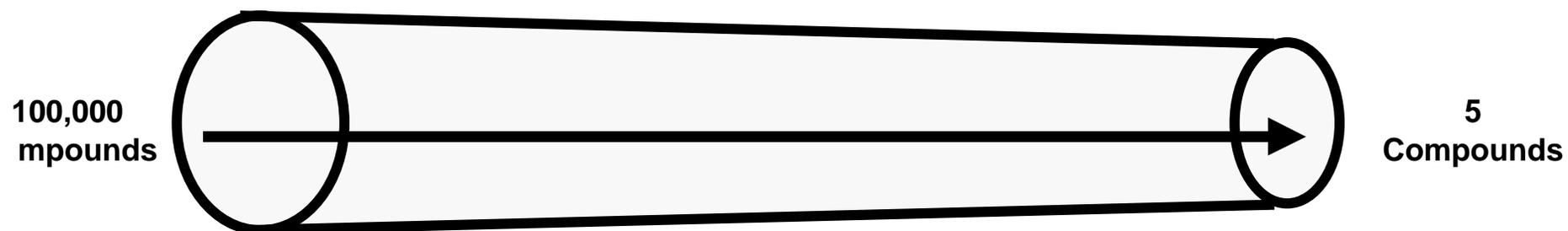
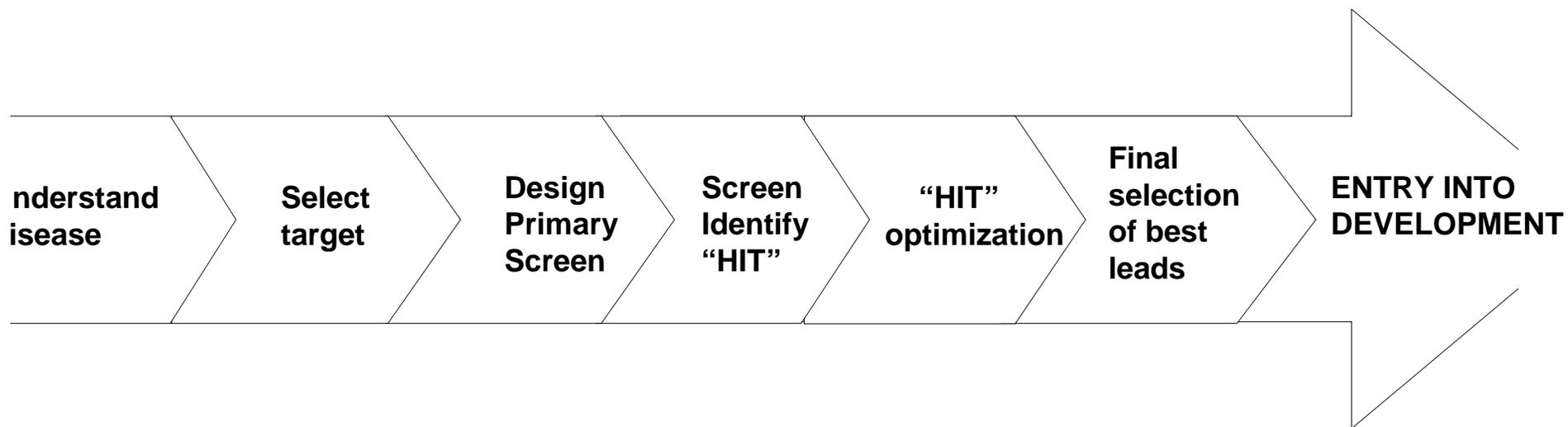
Protease Inhibitors Can be Effectively Delivered after Oral Administration



Critical Success Factors in Drug Discovery

- Access to large number of structurally diverse compounds for screening
- Availability of High Throughput Screening (HTS) based on relevant biological targets (unlimited capacity)
- Timely access to macromolecular structural information of biological targets to facilitate Structure Based Drug Design

Drug Discovery Funnel



“It is not the strongest of the species who survive, nor the most intelligent, but the ones most responsive to change.”

-- Charles Darwin